Cirrhosis

**Overview**

- Chronic & progressive liver disease
- Mechanism: hepatocyte destruction → replaced by scar tissues → fibrotic tissues causes blood flow resistance through liver
- Etiology

<table>
<thead>
<tr>
<th>Alcohol intake</th>
<th>↑Alcohol intake long term → steatosis → oxidative disease process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Hep C</td>
<td>Most common cause of liver transplant in US, about 30% with HCV develop cirrhosis in 20 years</td>
</tr>
<tr>
<td>NASH</td>
<td>Non-alcoholic steatohepatitis, very similar in presentation to alcoholic liver disease</td>
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<tr>
<td>Primary biliary cirrhosis</td>
<td>Immune-mediated destruction of intralobular bile ducts (e.g. pregnant women)</td>
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<tr>
<td>Hemochromatosis</td>
<td>Genetic disorder of inappropriate Fe absorption</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Genetic disorder of ↓Cu excretion</td>
</tr>
</tbody>
</table>

- Clinical presentation
  - Asymptomatic: insidious, don’t tend to notice until end stage
  - Non-specific: weight loss, nausea, abdominal discomfort, weakness, malaise
  - Liver-specific: hepatomegaly, jaundice, ascites
  - Dermatologic: caput medusa (swollen collateral blood vessels), spider angioma (large capillaries)
  - Lab values: ↑PTT, ↑INR, ↓clotting factor synthesis (factors I, II, V, VII, IX, X), ↓albumin, thrombocytopenia (due to splenomegaly and ↓thrombopoetin synthesis)

- Effects on the body
  - Altered mental status/com: liver cannot process toxins → ↑toxin accumulation that goes to brain
  - Secondary sexual changes: gynecomastia, testicular atrophy
  - Coagulation disorders: ↑INR, ↓platelets, ↑bleeding
  - Edema: ↑fluid accumulation in peritoneal cavity & extremities → ascites + edema
  - Hemorrhoids: swollen vessels in abdomen → bleeding → swollen hemorrhoids

- Classification
  - CHILD-PUGH
    - Not used much today except in dosing recommendations, too subjective
    - Score ≤6: Highly survivable
    - Score 7-9: Moderate disease
    - Score >9: End stage liver disease, require s transplant
  - MELD | Model for End Stage Liver Disease
    - Less subjective than CHILD-PUGH, based on objective data/labs (SCr, bili, INR), used more often today
    - Scores assess risk of death while awaiting transplants, correlates tightly with survival rates, used to determine who is at the top of the transplant list

**Complications of cirrhosis**

**Portal hypertension**

- Portal vein: very large blood vessel that drains blood from abdomen to the liver
  - Reason for first pass metabolism of drugs, helps filter out toxins
  - 25% of cardiac output @ 1-1.5L/min → sinusoids & hepatocytes → systemic circulation
    - Blood needs to go from portal vein through intricate system of hepatocytes to hepatic vein
    - Needs to expose as much blood as possible to the hepatocytes in order to clear toxins, metabolize products, and put important proteins and factors into the blood
  - As cells die due to cirrhosis & ↑fibrosis → easy for blood to back up and pool

- ↑Resistance x ↑Flow = ↑Pressure = portal hypertension
  - ↑Resistance: due to both fixed components + variable components
    - Fixed/nonreversible factors: fibrosis, physical blockage
    - Variable/reversible factors: vasoconstrictors e.g. endothelin or drugs
  - ↑Blood flow to portal vein
    - Vasodilation of splanchnic circulation: NO, PGEs, TNFα
    - ↑Na retention
- Expanded plasma volume
  - Mechanism: blood backs up in liver → body senses ↓ blood volume systemically → responds by producing vasodilators → worsens the pooling in the abdomen

- **Measuring pressure gradient:** $HVPG = WVP - FHVP$
  - $HVPG$: hepatic venous pressure gradient
    - Normally <5 mmHg
    - Portal hypertension when $HVPG \geq 6$ mmHg
  - $WVP$: wedge venous pressure → measures the hepatic sinusoid pressure (high)
  - $FHVP$: free haptic venous pressure → measures hepatic outflow pressure (low)

### Variceal Hemorrhage
- Life-threatening, often fatal, usually will rebleed if survive initial bleed
  - 50% resolve spontaneously, but still need to be treated as an emergency
  - 30% risk of death
  - 30-40% rebleeding risk within first 6 months
  - Greatest rebleeding risk within 48hrs
- **Portal hypertension** → need to relieve pressure → blood leaves through alternate routes i.e. collateral vessels → collateral vessels dilate → varices and other complications
  - Affects various veins:
    - Hemorrhoidal veins → ↑ hemorrhoids
    - Splenic veins → splenomegaly
    - Paraumbilical veins → caput medusa seen on skin of abdomen
    - Intrinsic vein of esophagus → varices, most worrysome
  - Varices arise when $HVPG > 8$ mmHg
  - Variceal hemorrhage occurs when $HVPG > 12$ mmHg
- **Endoscopy**: assesses the grade of severity (I-IV) and risk factors (large varices, cherry red spots, red wale marks)
- **Signs & symptoms of upper GI bleed**: weakness, fatigue, dizziness, hematemesis, melena

### Primary prevention
- Prophylaxis for patients with ≥ grade II
  - Goal: ↓ portal blood flow → ↓ portal hypertension → ↓ $HPVG$ → ↓ risk for bleeding
    - Goal: ↓ $HPVG < 12$ mmHg (but too invasive to measure routinely)
    - Goal: ↓ HR until bradycardic, but not < 55 bpm
  - First line therapy: non-selective β blockers
    - MOA: β₂ blockade → splanchnic vasoconstriction → ↓ portal blood flow → ↓ portal pressure
    - Agents: propranolol 20mg bid or nadolol 40mg qd (titrated to max dose)

### Treatment options
- **Medical procedures**
  - **Band ligation**: definitive therapy, requires repeat sessions due to rebleeding,
    - Procedure of choice of control of acute bleed and secondary prophylaxis
    - Mechanism: suction cup to pull varix away → place rubberband around varix → tissue dies
    - Risks: overall well tolerated, ulcers, dysphagia, chest discomfort
  - **Sclerotherapy**: definitive therapy, 2nd line, requires repeat sessions
    - Mechanism: injection of caustic agent directly into vessel → (+)thrombosis → scarring
    - Risks: ulceration, strictures, bacteremia
  - **Balloon tamponade**: short term only, when all else fails, high rate of rebleeding
    - Mechanism: pump up balloon → compresses against varices → stops bleeding
    - Risks: pulmonary aspiration, esophageal ulceration, esophageal perforation
  - **Shunting procedure: TIPS**
    - TIPS | transjugular intrahepatic portosystemic shunt
    - Used as salvage therapy when endoscopic procedures & pharmacologic options fail
    - Risks: hepatic encephalopathy, rebleed risk, stenosis of stent
- **Pharmacologic therapy**
  - Non-selective β-blockers: propranolol, nadolol
    - DOC for prevention (both primary and secondary)
  - Octreotide
    - Long acting somatostatin analogue, selective splanchnic vasoconstrictor, DOC for control of bleed
    - Dosing: 50mcg LD then 50mcg/hr infusion for 72hrs
- Risks: hypo-/hyper-glycemia, bradycardia, headache, abdominal cramping

**Vasopressin**
- Non-selective vasoconstrictor, less preferable than octreotide
- Very high dose needed: 0.4 U/min
- Risks: ischemia (used with nitroglycerin helps ↓risk), hyponatremia

**Nitrates**
- Used if β blockers are not tolerated, no longer recommended for primary prophylaxis
- MOA: ↓intrahepatic resistance → reflex splanchnic vasoconstriction → ↓portal blood flow
- Risks: systemic vasodilation, ↓arterial pressure, ↓CO, ↓renal function

<table>
<thead>
<tr>
<th>Summary</th>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prophylaxis</strong></td>
<td>Non-selective β-blockers (if ≥grade 2)</td>
<td>Band ligation if huge varices</td>
</tr>
<tr>
<td><strong>Control of acute bleed</strong></td>
<td>Band ligation + octreotide</td>
<td>TIPS (salvage therapy)</td>
</tr>
<tr>
<td><strong>Secondary prophylaxis</strong></td>
<td>Band ligation + non-selective β-blockers</td>
<td>TIPS or transplant (salvage therapy)</td>
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</table>

**Ascites**
- Most complication of cirrhosis, indicator of poor prognosis, marker of progression
- **Clinical presentation:** ↑abdominal girth, ↑weight, ↑abdominal pressure, SOB, difficulty ambulating, ↓balance = ↑falls

**Pathophysiology**
- Neurohormonal dysregulation → Na & H₂O retention (vicious cycle)
- ↑Blood flow to splanchnic bed → excess lymph fluid production
- Portal hypertension: shifts fluid from hepatic/splanchnic interstitium into intraperitoneal cavity → fluid accumulation (nowhere else to go) + sometimes pleural effusion

**Diagnosis**
- Paracentesis (30-50mL) → identify cause of ascites, diagnose infection if present
- SAAG | serum-ascites albumin gradient
  - SAAG = [serum albumin] − [ascites albumin] >1.1mg/dL is consistent with portal hypertension

**Treatment**
- Cautious incremental removal of fluid: too rapid → hypovolemia, kidney failure risk, hypotension, dehydration
- **Non-pharmacologic therapy**
  - Complete abstinence from alcohol
  - Sodium restriction: <2g/day, <88mEq/day
  - Fluid restriction: 1-1.5L/day only if dilutional hyponatremia (Na <125)
  - Large volume paracentesis (LVP): >4L fluid
    - Used in tense ascites, refractory ascites, to improve SOB
    - Not recommended due to risks: hypotension, renal failure, intestinal perforation, death, infection
    - Albumin infusions (7g per L removed): may be used to beef up peritoneal space
  - Shunts: TIPS
    - Used in refractory ascites that requires frequent LVP (≥q2weeks)
    - Risks: infection, shunt thrombosis, encephalopathy, very invasive

- **Pharmacologic therapy: diuretics**
  - Goal: ↓ascites without ↓intravascular volume
  - **Spironolactone (DOC)**
    - MOA: K⁺ sparing diuretic that competitively inhibits aldosterone
    - Weak in normal patients but very effective in cirrhotic patients
    - Dose: 100mg daily (max 400mg/day)
    - SE: hyperkalemia, hyponatremia, gynecomastia, impotence
  - **Furosemide**
    - MOA: loop diuretic with rapid natriuretic effect
    - Not as effective as spironolactone, but often use both in combination, maintains K⁺ homeostasis
    - Dose: initially 40mg/day → maintain ratio of 100mg:40mg for spironolactone: furosemide
  - **Amiloride**
    - MOA: K⁺ sparing diuretic that does not inhibit aldosterone (not as effective, not 1st line)
    - Dose: 10mg amiloride may be used to replace 100mg spironolactone
  - Monitoring efficacy of diuretics
    - Daily weights (1kg = 1L): ↓0.5kg/day if no edema, ↓1kg/day if peripheral edema
Urine output: output > input by 0.5-1L/day
Abdominal girth measurements
- Common SE: volume depletion, hypotension, renal impairment, K⁺ imbalance, hyponatremia, alkalosis

**SBP | Spontaneous bacterial peritonitis**

- **Bacterial translocation**: bacteria escape intestinal wall → cross lymph nodes → enter ascites fluid → colonization
- **Typically monomicrobial**: *E. coli*, *Klebsiella*, *Streptococcus* are the most common
- **Diagnosis & treatment** based on culture and PMN count >250 cells/mm³ in fluid sample (neutrocytic)

<table>
<thead>
<tr>
<th>Specific to cirrhotic patients</th>
<th>Spontaneous bacterial peritonitis</th>
<th>Monomicrobial culture pos + neutrocytic</th>
<th>Treat depending on culture: GNR, strep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>Monomicrobial culture neg + neutrocytic</td>
<td>Empirically treat with normal SBP therapy</td>
</tr>
<tr>
<td></td>
<td>Monomicrobial non-neutrocytic bacterascites</td>
<td>Monomicrobial culture pos + non-neutrocytic</td>
<td>Treat with SBP therapy if symptomatic</td>
</tr>
</tbody>
</table>

Treatment:
- ³rd generation cephalosporin: cefotaxime 2g q8h or ceftriaxone 2g q24h x 5 days
- If allergic use an IV fluoroquinolone: levofloxacin 600mg q24h

<table>
<thead>
<tr>
<th>Not specific to cirrhotic patients</th>
<th>Secondary bacterial peritonitis</th>
<th>Polymicrobial culture pos + neutrocytic + symptoms (glucose&lt;50, LDH&gt;225, TP&gt;1)</th>
<th>Broader treatment: GNR, enterococcus, anaerobes (e.g. imipenem)</th>
</tr>
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<tbody>
<tr>
<td>Polymicrobial bacterascites</td>
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**Prophylaxis**: antibiotics and duration of therapy based on risk factor

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Antibiotics</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Previous SBP episode</td>
<td>Cipro 500mg QD + levo 250mg QD + Bactrim DS 5-7 days/week</td>
<td>Lifelong</td>
</tr>
<tr>
<td>GI bleeding with ascites</td>
<td>Cipro 500mg BID + levo 500mg QD + ceftriaxone 1g q24h</td>
<td>7 days</td>
</tr>
<tr>
<td>Ascites protein &lt;1g/dL</td>
<td>Cipro 500mg QD + levo 250mg QD</td>
<td>During hospital stay</td>
</tr>
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</table>

**Hepatic encephalopathy**

- **Clinical presentation**: intellectual deterioration, reversal of sleep cycles, altered personality, lethargy, somnolence, coma
- **Indicator of poor prognosis**
- **Pathophysiology**: damaged hepatocytes + shunting of portal blood → liver unable to clear toxins
- **Neurotoxins implicated**: NH₃, BZD-like compounds, AAAs, false NTs, mercaptans, Mn, short chain Fas, phenols
  - NH₃ levels and BZD levels do not correlate with degree of encephalopathy severity
  - NH₃ produced from metabolism of Gln to Glu → excess NH₃ leads to excess Glu in CNS
  - BZDs: produced in GI tract by bacteria, bind to GABA receptors enhancing inhibitory actions
  - AAA: Tyr, Trp, Phe → converted into false NT that inhibit neural function
  - False NT: octopamine, phenylethanolamine
- **Precipitating factors**: GI bleed, infection, constipation, psychoactive drugs, TIPS, shunts, dehydration, diuretics, renal failure, electrolyte imbalances, large protein meal
- **Treatment: lactulose**
  - MOA: non-absorbable disaccharide → metabolized by gut bacteria into lactice, acetic, & formic acids → ↓colonic pH → traps NH₄⁺ & (→)viability of toxin-producing bacteria
  - Dosing
    - Acute encephalopathy: 30-45mL q2h until diarrhea (PO or NG) or as enema
    - Chronic encephalopathy: titrate dose to maintain 2-4 loose stools/day → about 30mL BID-QID
    - SE: diarrhea, flatulence, abdominal cramping, excessively sweet taste, dehydration, electrolyte imbalance
- **Antibiotics**
  - Used to ↓NH₃ and toxin load in colon
  - Agents: metronidazole, rifaximin, neomycin

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Metronidazole 250mg po BID</th>
<th>Nausea, metallic taste, disulfiram reaction with alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin 550mg po BID</td>
<td>Expensive ($1200/month)</td>
</tr>
<tr>
<td></td>
<td>Neomycin 500-1000mg po BID</td>
<td>Renal toxicity &amp; ototoxicity with chronic therapy</td>
</tr>
</tbody>
</table>
Hepatorenal syndrome

- Renal failure caused by altered hemodynamics due to portal hypertension
  - Splanchnic & systemic vasodilation
  - Arterial underfilling $\rightarrow$ poor renal perfusion
  - Activation of RAAS, SNS, and antidiuretic hormone
  - Vasoconstriction at kidney $\rightarrow$ ↓GFR

- Diagnosis of exclusion
  - Severe cirrhosis with CrCl < 40mL/min or SCr > 1.5mg/dL
  - R/O: shock, infection, nephrotoxic drugs, hypovolemia, obstruction, intrinsic kidney disease

- Two categories

<table>
<thead>
<tr>
<th>Type</th>
<th>Rapid process</th>
<th>Gradual</th>
<th>Therapy serves as bridge to transplant</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>SCr doubling to &gt;2.5 in &lt;2 weeks</td>
<td>↓GFR to SCr &gt;1.5</td>
<td>Octreotide 100-200mcg SQ q8h</td>
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<td></td>
<td></td>
<td></td>
<td>Midodrine 7.5-12.5mg po q8h</td>
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<td>Albumin 20-40g/day</td>
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<tr>
<td>Type 2</td>
<td>Often manifests as diuretic resistant ascites</td>
<td>Managed with Na restriction, diuretic avoidance, serial LVPs</td>
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